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Review

p38 MAP-Kinases pathway regulation, function and role in human diseases

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Abstract

Mammalian p38 mitogen-activated protein kinases (MAPKs) are activated by a wide range of cellular stresses as well as in response to inflammatory cytokines. There are four members of the p38MAPK family (p38α, p38β, p38γ and p38δ) which are about 60% identical in their amino acid sequence but differ in their expression patterns, substrate specificities and sensitivities to chemical inhibitors such as SB203580. A large body of evidences indicates that p38MAPK activity is critical for normal immune and inflammatory response. The p38MAPK pathway is a key regulator of pro-inflammatory cytokines biosynthesis at the transcriptional and translational levels, which makes different components of this pathway potential targets for the treatment of autoimmune and inflammatory diseases. However, recent studies have shed light on the broad effect of p38MAPK activation in the control of many other aspects of the physiology of the cell, such as control of cell cycle or cytoskeleton remodelling. Here we focus on these emergent roles of p38MAPKs and their implication in different pathologies.

Keywords: p38 MAP kinase; Cellular stress; Pro-inflammatory cytokines; Cellular differentiation; Inflammatory disease; Cancer

1. Introduction

Cells respond to changes in the physical and chemical properties of the environment by altering many cellular functions such as survival, proliferative potential, metabolism rate, interaction with other cells, and numerous cellular processes involved in the homeostasis and health of the organism. These environmental changes include alterations in the concentrations of nutrients, growth factors, cytokines and cell damaging agents, but also physical stimulation mediated by changes in the osmolarity of the medium. In response to those changes, mammalian cells activate four well-characterised subfamilies of mitogen-activated protein kinases (MAPKs): ERK1/2, ERK5, JNKs and p38s. Integral to all MAPK pathways, are central three-tiered core signalling modules consisting of the following protein kinase families: MAPK kinase kinases (MKKKs), MAPK kinases (MKKs) and MAPKs. The MAPKs are activated upon dual phosphorylation of tyrosine and threonine residues in a conserved Thr–*Xaa*–Tyr motif (where *Xaa* is any amino-acid) in the activation loop of kinase subdomain VIII. MAPK phosphatases reverse the phosphorylation and return the MAPK to their inactive state. Phosphorylation of MAPKs is catalysed by the dual specificity kinases, MKKs, which are in turn activated upon phosphorylation of Ser/Thr residues, and are highly selective in phosphorylating specific MAPKs. The mechanism that accounts for the specificity of MKKs to activate individual MAPK isoforms is mediated, in part, by an interaction between an N-terminal region located on the MKK and different docking sites present on the MAPK, and also by the structure of the MAPK activation loop that contains the Thr–*Xaa*–Tyr dual phosphorylation motif [1–6]. The first component activated in the MAPK core signalling module are MKKKs which phosphorylate specific MKKs and have distinct motifs in their sequences that confers selectivity to their activation in response to different stimuli.

2. Identification of mammalian p38 MAP-kinases

There are four p38 MAP kinases in mammals: α, β, γ and δ. Among all p38 MAPK isoforms, p38α is the best characterised

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and is expressed in most cell types. p38α MAPK was initially identify as a 38 kDa polypeptide that underwent tyrosine phosphorylation in response to endotoxin treatment and hyperosmolarity shock [7]. p38α was the mammalian MAPK orthologue of Hog1, the osmosensing MAPK of *Saccharomyces cerevisiae* [8]. In parallel, two other groups independently identified p38α as a kinase activated by stress (also called Reactivating Kinase, RK) [9] and IL-1 (named p40) [10] that could directly phosphorylate and activate the Ser/Thr protein kinase MAPK-activated protein kinase 2 (MAPKAP-K2), which, in turn, phosphorylates the small 27 kDa heat shock protein, HSP27 [10–12]. Later on that year, another identification of p38α was reported, this time as a polypeptide receptor for a class of pyridinyl imidazole anti-inflammatory drugs, called cytokine-suppressive anti-inflammatory drugs (CSAIDs), with SB203580 being the most extensively studied compound [13].

A few years after the identification of p38α, three additional isoforms were described encoded by different genes: p38β [14], p38γ (also called SAPK3 and ERK6) [15,16] and p38δ (also called SAPK4) [17,18]. Splicing of p38β has been also reported [19,20]. Although all p38 isoforms are widely expressed, p38γ is most significantly expressed in skeletal muscle and p38δ is mainly found in testis, pancreas, kidney and small intestine [17].

The p38 MAPK subfamily can further be divided into two distinct subsets, on the one hand p38α and p38β and on the other, p38γ and p38δ (see Fig. 1). This is evident firstly from their amino-acid sequence identity: p38α and p38β are 75% identical, whereas p38γ and p38δ are 62% and 61% identical to p38α, respectively. Of note, p38γ and p38δ are more identical (~70%) to each other. Secondly, their susceptibilities to inhibition at low concentrations by the compounds SB203580 and SB202190. *In vitro* and *in vivo* assays demonstrated that only p38α and p38β are inhibited by these compounds, whereas p38γ and p38δ were completely unaffected by the drugs [17,21,22]. The basis of this inhibition was revealed in the crystal structure of p38α complexed with SB203580. Thr106 in the hinge of the p38α and p38β ATP binding pocket interacts with a fluorine atom in the SB203580 structure. This orients the drug to interact with His107 and Leu108 of the pocket preventing ATP binding [23,24]. p38γ and p38δ possess Met, a large side chain amino acid, at the Thr106 equivalent position in the ATP binding pocket that prevents inhibitor binding. Substitution of residue Thr106 in p38α, alone or in combination with His107 or Leu108, with the corresponding more bulky residue from p38γ or p38δ (Met and Pro or Phe, respectively, in both cases) abolishes SB203580 binding. Conversely, if the amino acid of p38γ, p38δ, or even JNK1 which corresponds to p38α Thr106 is replaced with Thr, the resulting mutants display at least partial sensitivity to SB203580 [23,24]. A third difference between these two subgroups of p38MAPKs is with regard to substrate selectivity of these kinases. For example, microtubule-associated protein Tau is a better *in vitro* substrate for p38γ and p38δ than p38α and p38β [25,26], and this is also true for the scaffold proteins α1-syntrophin, SAP90/PSD95 and SAP97/hDlg [27–29]. Conversely, MAPKAP-K2, MAPKAP-K3 and glycogen synthase are better phosphorylated by p38α and p38β than p38γ and p38δ [17,21,30].

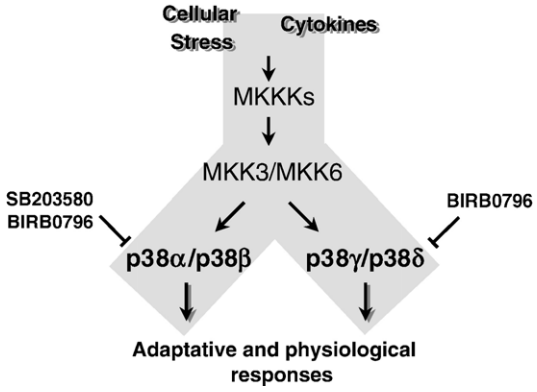

Fig. 1. p38 MAPKs signalling pathways.

3. Regulation of the p38 MAPK signalling module

3.1. Dual phosphorylation by MKKs

The p38 MAPKs are strongly activated *in vivo* by environmental stresses and inflammatory cytokines, and less by serum and growth factors. Together with the JNK family, p38 MAPKs are also known as Stress-Activated Protein Kinases (SAPKs). The canonical activation of p38 MAPKs occurs via dual phosphorylation of their Thr–Gly–Tyr motif, in the activation loop, by MKK3 and MKK6 [31], [32]. Upon activation, the dually phosphorylated p38 MAPK goes through characteristic global conformational changes that alters the alignment of the two kinase halves (N-terminal and C-terminal domains) of the folded protein and enhances access to substrate, which together increases enzymatic activity [33,34].

MKK3 and MKK6 (also called SKK3) are highly selective for p38 MAPKs and do not activate JNKs or ERK1/2 [21,35–37]. The importance of these two kinases physiological function comes from knockout studies, where mice lacking both MKK3 and MKK6 are not viable, dying in midgestation with defects in the placenta and the development of the embryonic vasculature [38]. This observation indicates that MKK3 and MKK6 have some redundant roles, because loss of either gene alone yields healthy mice [39–41]. Using MKK targeted gene disruption and siRNA approaches, it has been shown that in response to most stimuli MKK3 and MKK6 are the main MKKs activating p38α, although in some circumstances, such as ultraviolet radiation, MKK4, an activator of JNK, may contribute to the p38α activation [38]. The major MKK required for p38 activation may not only be affected by the stimuli, but also by cell type as their level of expression varies. For instance, MKK3 has been shown to be the major p38 activator in mesangial cells stimulated by transforming growth factor [42], while MKK6 appears to be the predominant isoform in thymocytes [40]. Although, unlike p38α, the activation of p38β, γ and δ isoforms has not been extensively examined in MKKs knockouts, it has been suggested that the pattern of downstream p38 MAPK activation in the particular response may be

determined by the level of MKK6 activity, which activates all p38 isoforms *in vitro*, triggered by a given stimulus [43].

MKK6 and MKK3 are in turn activated by phosphorylation by a MAPK kinase kinase (MKKK). The MKKK responsible for activating the p38 MAPK pathways appears to be cell type and stimulus specific. Several MKKKs have been implicated in the regulation of p38 MAPK signalling, these include MLKs, ASK1, TAK1 and some members of the MEKK family [32,44–47]. Contributing to p38 activation upstream of MKKK are the low molecular weight GTP-binding proteins from the Rho subfamily such as Rac1, Cd242, Rho and Rit [48–50] and heterotrimeric G-protein coupled receptors [51].

3.2. Autophosphorylation

Recently, it has been shown that, despite p38 MAPK pathway is normally regulated by MKKK–MKK pathway in mammalian cells, two other possible mechanisms of activating p38α have been proposed. In a yeast two-hybrid screen TAB1 (Transforming growth factor-β-activated protein 1 (TAK1)-binding protein 1) was identified to bind to p38α MAPK [52], but not to interact with other p38 family member. During the past 4 years, some studies have established that this adaptor protein represent an example of MKK-independent activation of p38 MAPK implicated in the ischemic heart and immunological processes [53–55]. This MKK-independent activation is achieved through the autophosphorylation and activation of p38α after interaction with TAB1 [52]. This mechanism appears to be involved in the AMPK activation of p38α in ischemic heart [56]. Intriguingly, in cardiomyocytes it was observed that although TAB1 lead to an increase in p38α activity, none of the classic downstream activities of the enzyme (associated with the activation of p38α by MKKs) were observed [57]. The authors of the study found that TAB1 sequestered p38α to the cytosol and this could be a mean of preventing some of the MKK-activated p38α functions. It remains to be demonstrated how widespread this model of activation is and if it leads to any cellular functions of p38α. However, this mechanism does not contribute to p38 MAPK activation in fibroblasts or epithelial cells under the same conditions [38,44].

Another MKK-independent mechanism of activation of p38α has been observed in T cells stimulated through the T cell antigen receptor (TCR). In this system, p38α is activated by an alternative mechanism in which TCR-mediated stimulation activates proximal tyrosine kinases that results in the phosphorylation of p38α on a noncanonical activating residue, Tyr323. This phosphorylation activates p38α, probably by causing changes in its structural conformation, to phosphorylate third party substrates as well as its own Thr–Gly–Tyr motif [58,59].

3.3. p38 scaffold and binding proteins

The protein kinases that form the MAPK signalling modules may interact via a series of sequential binary interactions to create a protein kinase cascade. However these protein kinases may be organized into signal complexes to create a functional MAPK module. This organization may be mediated by the interaction of the protein kinase with one member of the cascade or, alternatively, by a scaffold protein that interacts with each of the protein kinases. Although a number of scaffold proteins have been implicated in the regulation of different MAPK signalling modules [60], not many have been found to participate in the p38 MAPK cascade. One example, is the protein Osmosensing Scaffold for MEKK3 (OSM) which forms a complex with Rac, MEKK3 and MKK3 in the activation of p38α in response to hyperosmotic stress [61]. OSM could be the mammalian counterpart of STE50 in *S. cerevisiae*, which is required for the regulation of Hog1 under the same stress [62]. Similar roles in the activation of the p38 MAPK pathway have also been proposed for the members of the JNK-interacting protein (JIP) family JIP2 and JIP4, which are scaffold proteins for the JNK pathway [60]. JIP2 can bind to JNK and to the other components of this pathway, MKK7 and MLK3 [63], but also binds to MKK3, p38α and p38δ MAPKs [64–66]. On the other hand, JIP4 also binds to JNK but not to MKK7 or MLK3, and its function is different to other JIP proteins, it does not affect the activation of JNK pathway. In contrast, JIP4 appears to be a new component of the p38 MAPK pathway since it is an activator of this cascade by a mechanism that requires MKK3 and MKK6. JIP4 interacts with p38α and p38β, but not with p38γ or p38δ [60,67].

TAB1, as mentioned previously, has been linked with a novel way of activating p38α, but, in contrast, it was also found that TAB1 complexed with TAK1 and TAB2 or TAB3 can mediate a negative feedback loop following phosphorylation by p38α of TAB1 in response to inflammatory stimuli [44].

3.4. Downregulation of p38MAPK pathway

The magnitude and duration of p38 MAPK signal transduction are critical determinants of its biological effects. Activation of p38 MAPK occurs within minutes in response to most stimuli and is transient. This suggests that p38 MAPK functions as a biological switch that must be downregulated, both under basal conditions and during adaptation. In mammalian cells several protein phosphatases interact with and inactivate p38 MAPK pathway, both PP2C (Ser/Thr phosphatase) and PTP (Tyr phosphatase) have been shown to regulate p38 MAPK [68, 69]. Moreover, another family of dual-specificity phosphatases plays a key role in the regulation of these MAPKs, since, for example, the M3/6 and MKP-7 phosphatases have been shown to regulate JNK and p38 MAPKs [70,71].

4. Downstream targets and some physiological roles of the p38 MAPKs

4.1. Downstream targets for p38 MAPKs

The identification of physiological substrates for p38α and p38β has been facilitated by the availability of relatively specific pyridinyl imidazole inhibitors such as SB203580 and SB202190 [11,72]. These compounds have been very important tools for the delineation of pathways in which these MAPKs are

involved. However, because they inhibit both kinases, p38α and p38β, with similar IC_{50} values, it is not possible to distinguish between the effects of either MAPK or other kinases also inhibited by these inhibitors with similar potency [73]. This problem can be partly solved by the use of mice-deficient for each p38 MAPKs. Knockout mice for p38α have been generated, but they die at midgestation [74–76], whereas tissue-specific knockouts have implicated p38α in cardiomyocyte proliferation and survival [77,78]. Recently p38β, p38γ and p38δ and double p38γ/p38δ knockout mice have also been generated, which are viable and fertile [28,79]. Moreover, the diaryl urea compound BIRB796 [80] is not only a potent inhibitor of p38α and p38β, but also inhibits p38γ and p38δ at higher concentrations in cell-based assays providing a new tool for identifying physiological roles of these two p38 MAPK isoforms by using varying concentrations of this new compound in combination with the pyridinyl imidazoles [22].

Many p38 MAPK targets have been described, both in the cytoplasm and in the nucleus, which indicates that multiple cellular functions are under their control. p38α MAPK was shown to be present in both the nucleus and the cytoplasm of quiescent cells, but upon cell stimulation, some evidence suggests that it translocates from the cytoplasm to the nucleus [81]. However, other data indicate that activated p38 MAPK is also present in the cytoplasm of stimulated cells [82]. p38 MAPK are proline-directed kinases. However, substrate specificity is not only determined by the targeted amino acids but also by specific docking domains present on the substrate protein and by specific substrate binding motif in the p38 MAPK. Thus, although the substrate specificity of all p38 MAPK isoforms is known to overlap, there are some differences between the two subgroups of p38 MAPKs with regard to substrate selectivity of these kinases.

Some p38α and p38β physiological substrates are summarised in Fig. 2, these have been shown to be transcription factors, other protein kinases which in turn phosphorylate transcription factors, cytoskeletal proteins, and translational machinery components, and other proteins such as metabolic enzyme, glycogen synthase or cytosolic phospholipase A2 [30,32,83].

p38γ and p38δ MAPK isoforms can phosphorylate typical p38 MAPK substrates such as the transcription factors ATF2, Elk-1 or SAP1. However, they cannot phosphorylate MAPKAP-K2 or MAPKAP-K3, which are good substrates for the other two p38 MAPK isoforms [17,21]. A feature that makes p38γ unique among the p38 MAPKs is its short C-terminal sequence -KETXL, an amino acid sequence ideal for binding PDZ domains in proteins. p38γ binds to a variety of these proteins, such as α1-syntrophin, SAP90/PSD95 and SAP97/hDlg, and under stress conditions is able to phosphorylate them and modulate their activity [27–29]. These proteins are scaffold proteins usually targeted to the plasma membrane cytoskeleton

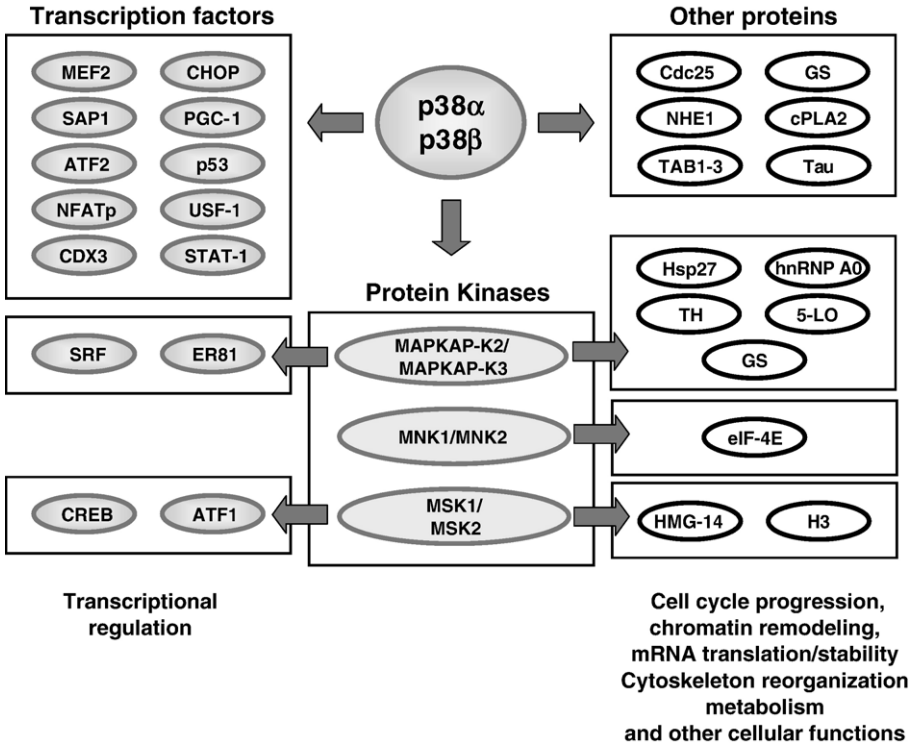

Fig. 2. Substrates and function of the p38α/β MAPKs, and of their substrates. The list of substrates indicated in this figure is not complete but shows the many important substrates and physiological roles described for these kinases to date. CHOP, CCAAT/enhancer-binding protein-homologous protein; MEF, myocyte enhancing factor; PGC, peroxisome proliferators activated receptor γ coactivator; SAP, serum response factor accessory protein; HBP, high mobility group-box transcription factor; NFAT, nuclear factor of activated T-cells; ATF, activating transcription factor; MAPKAP-K, mitogen activated protein kinase activated protein kinase; MSK, mitogen and stress activated protein kinase; MNK, mitogen activated protein kinase-interacting protein; TAK, transforming growth factor-β-activated kinase.

at specialised sites such as the neuromuscular junction and gap junctions through protein–protein interactions. In the case of SAP97/hDlg its phosphorylation by p38γ provided a mechanism of dissociating SAP97/hDlg from the cytoskeleton [28].

On the other hand, p38δ possibly plays a role in cytoskeleton regulation as it has been reported to phosphorylate the cytoplasmic protein stathmin which has been liked to regulation of microtubule dynamics [84]. Microtubule-associated protein tau is another protein substrate of p38δ [25,26]. Eukaryotic elongation factor 2 (eEF2) kinase was identified in a screen for substrates for p38δ and shown to be inhibited upon phosphorylation on Ser359 [85,86]. Moreover, it has been suggested that p38δ regulates involucrin gene expression through the transcription factor CHOP [87,88].

4.2. Roles of p38 MAPKs in cellular differentiation

Evidences from a number of studies carried out during the past few years establish a key role for the p38 MAPK pathway in the conversion of myoblasts to differentiated myotubes during myogenic progression [89–92]. Myogenic differentiation proceeds through irreversible cell cycle arrest of myoblasts followed by a gradual increase in expression of muscle-specific genes. The persistent activation of p38 MAPK, induced at early stage of this process, leads to upregulation of myogenic markers and accelerates myotube formation in cell culture models. Treatment with the p38α/β inhibitor SB203580 blocks fusion of myoblasts to myotubes, as well as the induction of muscle-specific genes, [89–92], whereas activation of p38 MAPK by over-expression of a constitutively active mutant of its activator MKK6 (MKK6-EE) is sufficient to stop cell proliferation and to induce both the expression of differentiation markers and the appearance of multinucleated myotubes [91,93]. Recent *in vivo* studies demonstrated that p38 MAPK signalling is a crucial determinant of myogenic differentiation during early embryonic myotome development [94].

p38 MAPK controls progression of myoblasts differentiation at multiple levels: transcription factor activity, chromatin remodelling and turnover of mRNAs encoding certain regulators of muscle differentiation. Different reports have shown that p38α and p38β phosphorylate and enhance the transcriptional activity of members of the myocyte enhancer factor-2 (MEF2) family, MEF2A and MEF2C, but not MEF2D [95–97]. By contrast, p38γ only weakly phosphorylates MEF2A, MEF2C and MEF2D *in vitro* and barely stimulates their transcriptional activities *in vivo*, whereas p38δ does not phosphorylate any of them [51,91]. MEF2 factors cannot activate muscle gene on their own, but they do potentiate the activity of basic helix–loop–helix myogenic regulatory factors (MFRs), which control the activation of muscle differentiation-specific genes, and their transcriptional co-activators, including a chromatin remodelling enzyme [98,99]. Moreover, the phosphorylation of the protein E47 by p38 MAPK, which is a partner of MyoD (a MRF family member), promotes functional MyoD-E47 hetero-dimerization, and targets chromatin-remodelling enzymes SWI/SNF and RNA polymerase II to muscle-specific loci [91,92,97,99–101], thereby inducing transcription of muscle specific genes. One recent study has reported evidences that p38 MAPK may control expression of specific set of muscle-specific genes acting not only at transcriptional level, but also on mRNA turnover. Thus, activation of p38 MAPK in myoblasts causes stabilization of some muscle-specific mRNAs by phosphorylating the AU-rich element (ARE)-binding protein KSRP, which controls the turnover of several transcripts during the transition from myoblasts to myotubes [102].

In addition to the promyogenic role of p38 MAPK at early myogenic stages, an unexpected repressive p38 MAPK function, which operates at late stages of muscle differentiation, has also been described using different approaches [93,103].

Most of the work that demonstrates the requirement for p38 MAPK in myogenesis is based on the use of the compound SB203580, which only inhibits p38α and p38β. The contribution of the different p38 MAPK family members to the differentiation process has been recently examined using mice lacking individually one of the four p38 MAPKs [104]. This study shows that p38α plays a central role in myogenesis, since myoblasts from mice lacking this kinase, but not those lacking p38β or p38δ, do not differentiate to multinucleated myotubes [104]. Given that p38γ expression is exceptionally high in skeletal muscle in comparison to other tissues and that, endogenous p38γ protein levels increase as myoblast differentiate into myotubes [89,105], it is not surprising that it may play a cardinal role in skeletal muscle differentiation. Indeed, Lechner et al. [15] initially showed that over-expression of p38γ in skeletal muscle cells leads to differentiation from myoblast to myotubes, and that a dominant-negative mutant of p38γ prevented this differentiation process. In addition, p38γ-deficient myoblasts show attenuated fusion *in vitro* although no major alteration was detected on neonatal or adult muscle [104] [C. Feijoo and A. Cuenda unpublished results], suggesting a possible compensatory mechanism due to the redundancy of functions among the p38 isoforms.

Some reports have suggested a role for p38δ in keratinocyte differentiation by regulating the expression of involucrin, which is a protein expressed during keratinocyte differentiation [106]. Keratinocyte differentiation is a multistage process that is initiated in the proliferative basal layer of the epidermis and proceeds through the metabolically active spinous and granular layers, until the cell is released from the cell surface at the cornified envelope [106]. It has been shown that activation of exogenously expressed p38δ by differentiation-inducing agents such as a bioactive green tea polyphenol (EGCG), okadaic acid (OA) or the phorbol ester TPA, correlated with increased involucrin promoter activity in keratinocytes via increased activity at AP1, Sp1 and C/EBP sites [107,108]. Of note, this occurred in an SB203580-independent manner and what is more, p38γ is not expressed in keratinocytes [87], although the mechanisms by which p38δ may regulates keratinocyte differentiation is still unknown. However, the regulation of keratinocyte differentiation does not seem to be exclusive for p38δ, thus it has been shown that treatment of keratinocytes with agents to deplete cholesterol, induces the upregulation of involucrin mRNA in a p38α-dependent manner, but not by p38δ [109]. Moreover, in the presence of exogenous constitu-

tively active MKK6 or MKK7, a role of p38α has also been identified [87].

On the other hand, it has been also claimed that p38δ may have a dual role in keratinocytes contributing not only to the differentiation process, but also to their apoptosis in a PKCδ dependent manner, and in response to OA or H_2O_2 [108, 110]. It is important to notice that most of the evidences involving p38δ in regulating keratinocyte differentiation or apoptosis are based in overexpression experiments, and require verification using other tools to both, inhibit the activity or the expression of different p38 MAPKs.

Other differentiation processes, in which p38 MAPKs have been shown to be implicated in either positive or inhibitory roles are: early stages of osteoclastogenesis from bone marrow precursors [111,112], adipogenesis [113,114], intestinal epithelial cells differentiation [115,116] and neuronal plasticity [117,118].

Interestingly, the number of studies highlighting the role of p38 MAPK pathway in stem cells differentiation is greatly increasing, although the mechanism underlying this role remains unknown. Thus, it has been reported that p38α/β MAPK function as a molecular switch to activate the quiescent satellite cells, which are muscle stem cells [119]. In addition, there are also evidences showing that in two different stem cell lines, the control of p38 MAPK activity also constitutes an early switch, committing stem cells into either neurogenesis or cardiomyogenesis [113]. Moreover, the differentiation of pancreatic progenitors to β-cells induced by the agent conophylline occurs through a p38 MAPK-dependent mechanism [120]. In hematopoietic stem cells (HSC), self-renewal is crucial for hematopoietic homeostasis. In this case it seems that activation of p38 MAPK by reactive oxygen species limits the life span of HSCs, a detrimental effect to their self-renewal capacity [121]. Thus inhibition of p38 MAPK may provide beneficial therapeutic target in some human diseases, as in aplastic anemia [122].

4.3. p38 MAPK pathways and cell migration

Another role for p38α that was first elucidated by using SB203580 is its involvement in chemotactic cell migration. It was first reported that SB203580 inhibited endothelial cell migration stimulated by vascular endothelial growth factor (VEGF) [123]. Subsequently, p38α was shown to relay chemotactic signals in numerous systems; N-formyl-L-leucyl-L-phenylalanine (fMLP) and C5a induced neutrophil migration [124,125], migration of vascular smooth muscle cells in response to PDGF, TGFβ and IL-1β [126,127], mast cells treated with stem cell factors [128], Gas6-Ark stimulated Gonadotropin-releasing hormone neuronal cells [129], epithelial cells stimulated with CXCL12/SDF1α, EGF, HGF, PDGF and TGFβ [130,131] and invasion of human breast epithelial cells by H-Ras [132]. The role of the four p38 isoforms in transducing chemotactic signals was evaluated using cells derived from mice lacking the different isoforms and the results demonstrated that only p38α but none of the other p38 isoforms were involved in relaying these signals [131]. Partial loss of pro-angiogenic (for example VEGF and HGF) signalling leading to increase cell migration could in part explain the embryonic lethality due to defect in labyrinth invasion by allantoic mesenchyme seen in the p38α-deficient mice [74,75]. It is worth noting that HGF-deficient mice also show a loss of proper organization in the labyrinth region. This can delineate a signalling pathway leading from tyrosine kinase receptors (c-Met and VEGFR2) to p21-activated protein kinase 1/2 [131] to p38α that regulates angiogenesis. Interestingly it is known that p38α is activated by hypoxia, a condition that leads to VEGF expression, which could also contribute to defective angiogenic signalling seen in p38α-deficient mice. The VEGF mRNA contains an ARE, and as mentioned previously, these sequences can be the targets of p38α-dependent regulation [133].

Most investigations on the role of p38α in cell migration have focused on links with the cytoskeleton rather than changes in gene expression. Initial studies have revealed that inhibition of p38α activity and the subsequent phosphorylation of HSP27 by MAPKAP-K2 could prevent actin cytoskeleton reorganization necessary for cell migration [123,126,134]. The role of the protein kinase MAPKAP-K2 in this pathway was confirmed in mice lacking this enzyme where vascular smooth muscle cells, fibroblasts and macrophages migration was all found to be impaired [127,131]. Interestingly, mice lacking MSK1 and MSK2, two other protein kinases that can be activated by p38α were found not to be involved in chemotactic cell migration [131]. Initial study on the role of the p38α-MAPKAP-K2 axis focused on HSP27. Unphosphorylated HSP27 has been shown to block actin polymerization and act as an actin cap-binding protein *in vitro*, which is modulated by phosphorylation [135–137]. Interestingly, at least two other substrates of MAPKAP-K2 could affect actin polymerization. CapZ-interactin protein (CAPZIP) as its name implies interacts with the actin cap-binding protein CapZ and is phosphorylated by MAPKAP-K2 [138]. Although the role of this protein in a model of cell migration has not been proven, it would possible to envisage that phosphorylation of CAPZIP could regulate the function of CapZ on actin polymerization. Recently, LIMK1 was shown to be phosphorylated and activated by MAPKAP-K2 in response to VEGF in endothelial cells [139]. LIMK1 induces actin remodelling by phosphorylating and inactivating cofilin, an actin-depolymerizing factor. Thus LIMK1 forms a crucial and integral part of the migratory response to VEGF in endothelial cells.

Caldesmon is an actin- and myosin-binding protein that is also involved in the assembly of actin filaments. It was found to be phosphorylated downstream of p38α in uPa-stimulated smooth muscle cells [140] and important for endothelial cell migration where it is abundantly found [141]. Paxillin is a phosphoprotein found at focal adhesions, crucial links between the extracellular matrix and the cell cytoskeleton. It was reported to be phosphorylated at Ser83 by p38α in NGF-stimulated PC12 cells [142]. Although it remains to be demonstrated that phosphorylation of Ser83 of paxillin is essential for cell migration, this provides another possible mechanism for p38α-dependent cell migration.

Another way, by which the p38α pathway can regulate angiogenesis and cell motility or invasion, is through the regulation of matrix metalloproteases called MMPs. Inhibition

of p38α MAPK activity with SB203580 was shown to block MMP-9 expression in phorbol myristate acetate (PMA)-treated human squamous cell carcinoma [143]. This was found to be also dependent on the transcription factor AP-1 [144]. In cells central to angiogenesis, like endothelial cells or macrophages, a similar role for the p38α MAPK has been proposed. In LPS-stimulated RAW macrophages, the same p38α MAPK-AP-1 pathway was shown to regulate MMP-9 expression [145]. This was also found to be the case in TNFα-stimulated monocytes [146]. In endothelial cells, sheer-stress induced MMP-9 expression was shown to be dependent on both the p38α MAPK and the ERK1/2 pathways [147]. Interestingly, MMP-9 expression correlates with severity of atherosclerosis [148], increasing the clinical interest of this MAPK pathway. In contrast to MMP-9, the regulation of MMP-2 in endothelial cells seems to be more dependent on the ERK1/2 MAPK than the p38α MAPK [149,150].

The importance of p38α in relaying chemotactic signals will be important for normal physiological functions like neutrophil migration and angiogenesis. However, this also raises the possibility of targeting p38α and its substrates involved in cell migration in situations where aberrant cell motility leads to disease development, like tumour growth (through angiogenesis), invasion and metastasis.

5. Pathological implication of the p38MAPKs

5.1. Role of p38MAPK pathways in inflammation

As mentioned above, p38α MAPK was first recognized for its role in inflammation in regulating the biosynthesis of pro-inflammatory cytokines, namely IL-1 and TNFα, in endotoxin-stimulated monocytes [13]. Subsequently it was found to be involved in regulating the production of IL-8 in response to IL-1 or osmotic shock [151] and the production of IL-6 in response to TNFα [152]. COX-2, another inflammatory mediator, was shown to be regulated at least in part by p38α [153–155]. p38α is thought to be the main isoform involved in mediating cytokine production as mice lacking p38β, the most closely related isoform, showed no defect in cytokine production or in immune function in an initial study [79]. Moreover, recently it has been shown that, in p38α deficient Th1 cells, the IFN-γ secretion stimulated by IL12/IL18 is defective compared with the secretion induced by TCR. Suggesting that the activity of p38α in Th1 cells may be restricted to one of the two pathways involved in IFN-γ production, [156]. No functions in inflammation for the other two isoforms of p38 MAPKs have been reported yet. Although regulation of these inflammatory mediators can arise at different levels, a lot of focus has been on the role of the p38α MAPK pathway in post-transcriptional regulation. These genes all share an ARE found in the 3′ untranslated region (3′UTR) of their mRNA. The presence of this element is known to shorten the half-life of the mRNA containing them and in some cases (as for TNFα) block their translation. The importance of this ARE found in the 3′UTR of TNFα mRNA in mediating the p38α regulation of translation has been elegantly demonstrated in a study of mice lacking the ARE of TNFα, where they became irresponsive to LPS-stimulated p38α-mediated TNFα translation [157]. In another mice model, this time lacking the protein kinase MAPKAP-K2, the downstream target of p38α, there is marked decrease in production of TNFα and IL-6 in response to LPS [158], which has also been linked to post-transcriptional regulation via the 3′ UTR ARE [159]. A similar regulation has also been observed for COX-2 [159]. Thus it seems that a common mechanism for the gene regulation by the p38α MAPK pathway is the post-transcriptional control via the ARE. The exact mechanisms by which p38α MAPK controls post-transcriptional regulation is still unknown and will most likely involve the phosphorylation and/or activation of numerous proteins. So far a number of substrates for MAPKAP-K2 could potentially be involved in post-transcriptional regulation; these include the ARE binding proteins TTP [160] and hnRNP A0 [161] and the poly (A)-binding protein PABP1 [162]. Moreover, hnRNP A1, an ARE binding protein as well, has been shown to be phosphorylated by MNK1, another protein kinase found downstream of p38α and to be important for TNFα production in T cells [163]. Furthermore, another ARE binding protein, KSRP has been shown to be directly phosphorylated at Thr692 by p38α. This phosphorylation blocks KSRP binding to the mRNA and therefore its destabilizing function [102].

Pro-inflammatory cytokine (PIC) production plays a key role in the pathogenesis of many chronic inflammatory and rheumatic diseases. In particular, TNFα, IL-1β and IL-6 are key players in rheumatoid arthritis, Crohn's disease (a subset of inflammatory bowel diseases), psoriasis, ankylosing spondylitis and chronic asthma [164–166]. Not only they are a cause of inflammatory diseases, but there is evidence that they play an important role in other diseases, including heart failure [167,168], ischaemic retinopathies [169] and the development of insulin resistance in diabetes [170]. Consequently, blocking the action of these PICs is an attractive therapeutic strategy. In view of this a number of pharmaceutical companies have developed drugs that target p38α MAPK in order to block PICs production. Some of these drugs have advance to human clinical trials. They include AMG 548 (Amgen), BIRB 796 (Boeringer Ingelheim), SCIO 469 and SCIO 323 (Scios, Johnson and Johnson) and VX-702 (Vertex). Although AMG 548 showed greater than 85% inhibition of ex-vivo LPS-induced TNFα and IL-1β in healthy males, its production was suspended due to random liver enzyme elevations that were not dose or exposure dependent [171]. Similarly BIRB 796 has shown some liver enzymes elevations that were above the upper limit of normal and there was no evidence for clinical efficacy of BIRB 796 in Crohn's disease in recent published results [172]. SCIO 469 is in phase II clinical trials for pain, multiple myeloma and rheumatoid arthritis and SCIO 323 is in phase I clinical trial for myelodysplastic syndrome, multiple myeloma, rheumatoid arthritis, cerebral ischemia and diabetes mellitus whereas VX-702 is a second generation inhibitor developed against inflammatory disorders that was designed to replace VX-745 shown to cross the blood–brain barrier [171]. However, in view of the many roles of p38α and the requirement of long-term treatment for chronic diseases, it is possible that downstream effectors or

specific upstream activators of p38α involved in PIC production may make better drug targets. This could explain in part why even with more than a hundred compound developed to inhibit this kinase none have found their way yet as a bona fide drug.

5.2. p38 MAPK pathways and cancer

During the last few years, members of the p38 MAPKs subfamily have joined the group of canonical signalling pathways involved in the transformation process. It has been shown that p38 MAPK pathway could be involved in some of the alterations observed in the physiology of transformed cells: self-sufficiency in growth signals, unlimited replication potential, protection against apoptotic cell death, de novo angiogenesis, and tissue invasion and metastasis [173].

One new role for the p38 MAPK pathway that has been elucidated in recent years is the regulation of checkpoint controls and cell cycle at G0, G1/S and G2/M transitions [174]. Depending on the cell type, p38 MAPK can either induce progression or inhibition at G1/S transition by differential regulation of specific cyclin levels (cyclin A or D1) as well as by phosphorylation of the retinoma protein (pRb), which is a hallmark of G1/S progression [38,174], and by phosphorylation of the p53 tumor suppressor on two activating sites in the N-terminal region (Ser33 and Ser46) [174–176]. On the other hand, activation of p38 MAPK in mammalian cells in response to various environmental insults, including ultraviolet (UV) light, disruption of the microtubule cytoskeleton, hyperosmotic stress and inhibition of histone deacetylase, initiates G2/M checkpoint [177–182], and G1 arrest following UV-induced DNA damage [183,184].

DNA damage checkpoints function as surveillance mechanisms during cell division to ensure that each step is completed properly, thus maintaining genetic integrity. In mammalian cells, the G2/M checkpoint response is complex and mediated by a number of signalling pathways, including the ataxia-telangiectasia mutated (ATM) and ATM-related (ATR) pathways [185] and, more recently, the p38 MAPK pathway [177]. Activation of the p38 MAPK signalling pathway, in response to stimuli that impose cell cycle arrest and/or cell death, results in the activation of its physiological substrate, MAPKAP-K2, which phosphorylates Cdc25B on Ser309 or Ser323 and Cdc25C on Ser216 [183]. This mediates the subsequent binding of 14-3-3 proteins and the shuttling of Cdc25B into the cytoplasm, which together induce G2 delay [177,179,183]. A specific inhibitor of p38 MAPK was shown to significantly reduce phosphorylation of Cdc25B on Ser309, which in turn significantly reduced Cdc25B-14-3-3 interactions and initiated the G2/M checkpoint response [177]. Cdc25s are protein phosphatases that activate cyclin dependent protein kinase activity (which is the major regulator of G2/M transition) [177]. More recently, p38 MAPK has been reported to block entry in S phase by phosphorylating CdC25A on Ser76 and Ser124 and of causing the degradation of Cdc25A protein in response to hyperosmotic stress and cytokine withdrawal in interleukin-7 (IL-7) and IL-3-dependent mouse lymphocytes [186,187].

Most of the work published on cell cycle regulation by p38 MAPK pathway has been focussed on studying the role of the isoforms p38α and β. In the case of p38γ, one report indicates its activation after ionizing radiation could be dependent on ATM [188]. However, all p38 MAPKs show robust induction by stresses such as UV radiation, whereas their induction by ionizing radiation is highly infrequent [189] [Y. Kuma, A. Cuenda unpublished results]. However, it has been shown that, *Xenopus* p38γ promotes meiotic G2/M transition in *Xenopus* oocytes treated with progesterone and activates XCdc25C by phosphorylating it at Ser205, whereas p38α or p38β have no effect [190]. Fully grown *Xenopus* oocytes are arrested in G2/prophase of meiosis I and are induced to proceed through meiosis by progesterone stimulation [190].

On the other hand, it has been shown that p38 MAPK is involved in the growth-inhibitory signalling cascade of contact inhibition in fibroblasts. This novel physiological function of p38α in cell cycle control provides further mechanism support for the idea that p38α may act as suppressor of tumorigenesis. Proliferation of non-transformed cells is regulated by cell-cell contact, which is referred to as contact-inhibition [191]. There is a sustained activation of p38α in response to cell–cell contact. Contact inhibition is impaired by p38α/β inhibitors as well as in p38α−/− fibroblasts. Moreover, p38α−/− fibroblasts show a higher saturation density compare to wild-type fibroblasts, which is reversed by reconstituted expression of p38α [191].

All these findings suggest that defects in p38α MAPK function may contribute to cell cycle defects and tumorigenesis. A clear example is the role of p38α in inducing terminal differentiation and inhibiting proliferation of rhabdomyosarcoma-derived cells, one of the more common solid tumors of childhood, as a consequence of defects in differentiation of muscle precursor cells. This defect is attributed to deficiency in p38 MAPK activity [192]. Another case of inhibition of tumorigenesis through p38 MAPK was reported in mice expressing the oncogenes ErbB2 or Ha-Ras, but disrupted for the gene Wip1 (also PPM1D), which encodes a phosphatase that inhibits p38 MAPK, manifested impaired mammary carcinogenesis [193,194]. Similarly, decreased p38 MAPK activity caused in cells by deletion of both upstream activators, MKK3 and MKK6, enhances proliferation of fibroblasts on low serum and increases tumorigenesis when immortalised MKK3/6 (−/−) fibroblasts (compared to wild-type cells) were injected subcutaneously in athymic nude mice [38]. Another phosphatase, DUSP26 (also known as MAPK-phosphatase 8) was shown to dephosphorylate p38 MAPK and promotes survival of anaplastic thyroid cancer cells [195].

Taken together these results clearly point to a role of the p38 MAPK activity in restraining uncontrolled cell proliferation. This was clearly established in a recent report demonstrating that a key role for the p38α MAPK in preventing tumorigenesis is to promote growth arrest and apoptosis specifically in response to reactive oxygen species (ROS) [196]. Dolado et al. showed that p38α-deficient cells are resistant to ROS-induced apoptosis and oncogenes that generate high levels of ROS leads to transformation of p38α-deficient MEFs. ROS can activate the MKKK ASK1, an upstream activator of the p38α MAPK, by dissociating it from the glutathione-S-transferase (GST) mu [197]. Alternatively, ROS could also activate p38α MAPK

through the inactivation of phosphatases by oxidation of the active site cysteine residue, consistent with the tumorigenic roles proposed for some p38α MAPK phosphatases previously mentioned [193–195]. Dolado et al. also showed that cancer cells have found ways to uncouple the activation of p38α MAPK by ROS by increasing levels of GST proteins. Thus, drugs that could restore this activation, by targeting GST proteins for example, could prove to be useful anti-cancer agents for certain tumours.

In contrast to the number of publications discussing the role of p38 MAPK pathway as a tumor suppressor, only a few publications have provided evidence for an oncogenic potential of this pathway [198]. This could involve supporting tumour growth and metastasis via the regulation of angiogenesis and cell invasion. Growth of tumors beyond a certain size results in hypoxia and requires the formation of new blood vessels for further growth, which is controlled through the production and secretion of angiogenic factors. p38α MAPK is activated by hypoxic conditions and is involved in the production of VEGF [133]. Interestingly, p38 MAPK also plays a role in the downstream signalling of VEGF leading to angiogenesis [199,200]. As mentioned previously, the p38α MAPK pathway was suggested to play a role in MMP-9 regulation, an observation initially made in a carcinoma cell line [143]. This suggests a potential role for the p38α MAPK pathway in promoting cell invasion and metastasis not only by mediating chemotactic signalling but also by controlling ECM remodelling. Interestingly, increase levels of angiogenic factors like VEGF and MMP-9 (that are both regulated by the p38α MAPK) correlate with unfavourable prognosis in many tumours.

There are now numerous reports supporting such hypothesis. In B-cell chronic lymphatic leukaemia cells constitutive expression of MMP-9 was dependent on p38α MAPK [201]. Interestingly, in contrast to what was observed in endothelial cells (see cell migration section) increase MMP-2 expression seem to be dependent on the p38α MAPK in many transformed cell lines. The TGFβ-mediated increase production of MMP-2 by prostate cancer cells involves the p38α MAPK–MAPKAP-K2–HSP27 axis [202,203]. Similar results were obtained in pre-neoplastic human breast epithelial cells whereas the TGFβ-stimulated MMP-2 expression was regulated by phosphorylation of ATF2 through the p38α MAPK signalling [204]. Similarly, in H-ras but not N-ras transformation of the same cell line, the production of MMP-2 was dependent on p38α MAPK but not the ERK1/2 MAPK [132,205]. Additionally, ras-dependent cellular invasion requires the p38α MAPK regulation of the serine protease urokinase plasminogen activator (u-PA) [206]. In human melanoma cells, the tetraspanin CD9 induces the expression of MMP-2 through the activation of both the p38α MAPK and the JNK pathway [207]. Thus, there seem to be an important role of the p38α MAPK pathway in up-regulating the expression of MMPs that correlates with an increased invasive phenotype of cancer cells. Now it will be important to understand the exact mechanisms by which the p38α MAPK pathway regulates these proteases. For example, does this regulation only occur at the transcriptional level via the ATF1 or ATF2 transcription factors or is the p38α MAPK pathway also involved in the translation and maturation of these proteases. This knowledge will hopefully increase the array of tools that can be used to disrupt the invasive phenotype of tumours.

Not only p38α but also other isoforms could mediate tumorigenesis. Recent data suggest that the oncogene Ras positively regulate expression of p38γ isoform and this may be involved in Ras-transformation in rat intestinal epithelial cells and in Ras-increased invasion in breast cancer cells [208,209].

5.3. p38 MAPKs in cardiovascular dysfunction

Cardiovascular mortality is an important health problem in human populations. Two leading causes of cardiac morbidity are pressure overload cardiac hypertrophy resulting from hypertension and cardiomyocyte apoptosis and necrosis following ischemic injuries. Shear stress from pressure overload can activate stress-activated protein kinases pathways [210], whereas both ischemia and reperfusion of isolated rat hearts lead to activation of p38MAPK and MAPKAP-K2 [211,212]. p38α was found to be the dominant p38 MAPK isoform found in the heart, with p38β levels undetectable and low levels of p38γ and p38δ [213]. Studies have proposed both a protective and damaging roles of p38MAPK in the stressed myocardium. This seemed to be dependent in part in the system studied. For example, in ischemia reperfusion, there is a difference in myocardial responsiveness between a mouse and a pig model; in that study p38 activation in the mouse contributes to acute cellular injury and death, while the same activation in pig has no causative effect [214].

The role of p38 MAPKs in cardiac hypertrophy has been suggested by studies using over-expressed active forms of their upstream activators MKK3 and MMK6 in cardiomyocytes. In these studies it was found that the active mutants elicited characteristic hypertrophic responses [210,215]. Moreover, over-expression of MKK3 in cardiomyocytes leads to an increase in apoptosis [210]. Interestingly, the differences between MKK3 and MKK6 can points to distinct roles of p38 isoforms, whereas the more restricted activation spectrum of MKK3 leading to increase apoptosis pointing to a role of p38α in promoting apoptosis. In a transgenic mice model using the same MKK3 and MKK6 constructs to activate p38 MAPK, it was found that p38 MAP kinase signalling can contribute to the loss of contractility and myocardium stiffness and promotes specific remodelling process in heart failure but there was minimal change in ventricular mass, suggesting that this pathway *in vivo* is not sufficient to induce hypertrophy, contrary to the report in cardiomyocytes [216]. Similarly, in a study using transgenic expression of dominant negative forms of MKK3, MKK6 and p38α in the heart, it was found that the p38 pathway can have an anti-hyperthropic effect and could function to restrain calcineurin-mediated hypertrophy through NFAT transcription factors [217]. However, a transgene expressing an active form of TAK1 in mice lead to increase p38α phosphorylation and cardiac hypertrophy, interstitial fibrosis, severe myocardial dysfunction, fetal gene induction, apoptosis and early lethality [218]. But over-expression of TAK1 not only activates p38α but JNK and NFκB [219], two pathways, which have themselves

been link to cardiac hypertrophy [210,220]. In studies of human hearts with either compensated hypertrophy or advanced heart failure, only in the latter case was there any detectable p38 activity [212]. It is conceivable that activation of the stress-activated pathway in the failing heart is an attempt to respond to shear stress but due to the weakness of the failing heart to adapt this activation might result in a more detrimental phenotype.

As mentioned above ischemia and reperfusion activates p38α MAPK and this protein kinase has been more extensively studied in this context. During ischemia in perfused heart, inhibition of p38MAPKs activity protects against hypoxic induced apoptosis and necrosis. Hypoxia was also found to lead to intracellular acidosis, which augments p38α activation and leads to apoptotic cell death [221]. Reactive oxygen species generated from the mitochondria during ischemia and reperfusion activates p38α MAPK and inhibition of p38α significantly prevented celled death arising from ischemia reperfusion [222]. In ischemia, AICAR and metformin (the latter two being specific activators of AMPK) treated cells, SB203580 blocked Bax translocation to the mitochondria, a hallmark of apoptosis, linking p38α activation by ischemia to increase cell death [223]. Thus the p38α MAPK has been linked with induction of pro-apoptotic signals. Similarly, MAPKAP-K2-deficient mice were found resistant to myocardial ischemic reperfusion injury, indicating that this protein kinase is also involved in transmitting pro-apoptotic signals [224]. However, a number of studies have proposed a role in cardioprotection for the p38 MAPK pathway. Protection due to ischemic pre-conditioning, the protection of myocardium conferred by cycles of brief ischemia–reperfusion, correlates with the activation and phosphorylation of p38α at Tyr182 in the rabbit heart [225]. It had been previously established that p38α was activated by cellular stresses like heat shock, oxidative stress or osmotic shock and that cellular resistance to these stresses were increased through enhanced actin cytoskeleton reorganization via the p38–MAPKAP-K2–HSP27 pathway [226,227]. In cardiac myocytes, activation of the p38α MAPK–MAPKAP-K2 and the subsequent phosphorylation of αB-crystallin, another member of the small heat shock protein family, provide protection against stress-induced apoptosis or PDGF-BB improved cardiac function following myocardial infarction [228,229]. A protective role for this pathway has been further supported by a study that showed that over-expression of MKK6 lead to an increased αB-crystallin levels and could explain the cardioprotective effect of MKK6 transgene over-expression [230]. An interesting explanation between these different results was suggested by a study where they found that p38 MAPK-mediated F-actin reorganization may stimulate apoptotic cell death but conversely can protect against osmotic-derived necrosis in cardiomyocyte [231]. Another study also found a similarly dual role of the p38α pathway where treatment with SB203580 aggravated myocyte necrosis but also revealed a cardioprotective role for the inhibition of p38α activity as it blocks contractility during reperfusion [232]. This effect on contractility was diminished as well in hearts of mice lacking MKK3 or MAPKAP-K2 when stimulated with TNFα [233]. Thus, although in various models inhibition of p38α leads to some degree of cardioprotection supporting a role for p38α in cardiac dysfunction [234–236] it is still unclear how this would apply to human clinical conditions and there is a need for greater research into appropriate targets of the p38 MAPKs. One attractive possibility would be to differentiate between targets of the p38α pathway that lead to apoptosis and those that protects against necrosis in order to develop drugs that only target the deteriorating branch of the p38α activity while maintaining the protection it confers.

5.4. Roles of p38 MAPK pathways in Alzheimer's disease

The pathological hallmarks of Alzheimer's disease (AD) are the accumulation of extracellular plaques and intracellular neurofibrillary tangles that are composed of filaments polymers of β-amyloid and the neuronal microtubule-associated protein Tau, respectively. It has been proposed that elevated levels of β-amyloid in AD brain induces microglial activation and consequent release of pro-inflammatory cytokines induced by the p38 MAPK pathway [237], which may contribute to the development of this pathology together with other disorders such as neuronal injury, trauma, ischemia and accumulation of oxidants with brain aging.

Another major hallmarks of AD, and other neurodegenerative disorders known as 'tauopathies', is the accumulation of neurofilaments made by the protein Tau [238]. The protein Tau belongs to the family of microtubule-associated proteins. Tau binds to β-tubulin and promotes microtubule assembly [239] playing major regulatory roles in the organization and integrity of the cytoskeleton network under normal physiological conditions. Tau is functionally modulated by phosphorylation, since the ability of Tau to bind and stabilize microtubules correlates inversely with its phosphorylation which may facilitates its self-assembly. Thus, when Tau is hyperphosphorylated (PHF-Tau), it dissociates from the cytoskeleton and aggregates itself. This PHF-Tau is the major component of the paired helical filaments (PHFs), which make up the neurofibrillary tangles that along with senile plaques, are the aberrant structures found in the brains of patients with AD [240–242]. This hyperphosphorylation could result from an increased activity of Tau kinases or the decreased activity of Tau phosphatases. In AD at least thirty serine/threonine residues are phosphorylated. Whereas numerous protein kinases have been shown to phosphorylate Tau and regulate its function *in vitro*, identification of the specific enzymes that regulate phosphorylation of Tau *in vivo* has proved difficult [25].

Given that more than half of the phosphorylation sites in PHF-Tau are serine and threonine residues followed by proline, it is conceivable that members of the MAPK family play an important role in phosphorylating Tau. Since aberrantly activated JNK and p38s have been reported to be associated with cells that contain filamentous Tau in some neurodegenerative diseases [243–245], these kinases may contribute to the hyperphosphorylation of Tau protein. Moreover, the p38MAPK activator, MKK6, has also been found to be active in neurodegenerative diseases [245]. Recently, all residues phosphorylated in Tau by each p38 isoform have been identified by radioactive ATP-labelling [25]. Using phosphospecific antibodies, it has been

demonstrated that these kinases phosphorylate Tau *in vitro* and that *in vivo* they are implicated in Tau phosphorylation in response to cellular stress [25,246,247]. In addition, p38s phosphorylate Tau on residues that are phosphorylated in PHF-Tau observed in AD brain [25,26], indicating that these kinases may contribute to the hyperphosphorylation of Tau protein in neurodegenerative diseases. In the last years it has been shown that Tau is a good *in vitro* substrate for the p38 isoforms p38δ and p38γ, and its phosphorylation by these two enzymes results in a reduction in its ability to promote microtubule assembly [25,26]. Moreover, overexpression of p38γ in neuroblastoma, induces Tau phosphorylation which correlates with a decrease in Tau associated to the cytoskeleton and an increase of soluble Tau [247]. It has been reported as well that p38δ is the major Tau kinase in neuroblastoma in response to osmotic shock [25]. All these evidences indicate that p38MAPKs can regulate Tau hyperphosphorylation in neurodegenerative disease and could be potentially good therapeutic targets for those diseases.

6. Concluding remarks

Most of the studies to date have focused on the role of the p38α isoform, which is widely referred as p38 in the literature. However, there are three other p38 isoforms (p38β, p38γ and p38δ) whose roles among the cellular functions and the implication in some of the pathological conditions described in this review have not been precisely defined so far. One important question that remains to be answered is whether these p38 MAPK isoforms are differentially activated by certain stimuli to mediate specific signals. Although, not many evidences exist so far, it is possible that for example, in the implication of p38 MAPK in cancer, some isoforms may play a pro-oncogenic role whereas other p38 isoforms act as tumor suppressors.

It is important to notice that the cell culture studies outlined here require confirmation using *in vivo* models like knockouts. Knockout mice for each p38 MAPK isoform have been generated, and except p38α knockout, which is lethal, the other knockouts lack of apparent phenotype. This may be due to the functional redundancy caused by the existence of highly related family members. This issue is demonstrated by Sabio et al. [28] using cells from mouse knockouts lacking multiple p38 family members in combination with the use of specific inhibitors for the different kinases. Such redundancy may account for the failure on finding a phenotype in the different p38 knockout mice and point to the need to generate knock-in mice expressing inactive p38MAPK and mice with tissue-specific inactivation of the individual p38MAPK family members. These mice, in combination with the use of specific new kinase inhibitors, should provide powerful biological models to address the specific roles of each p38MAPK isoform.

Studies carried out during the last few years have led to major progress in understanding the regulation of p38MAPKs and their functions *in vivo* (Fig. 3). In particular, the use of kinase inhibitors together with cells from genetically modified mice lacking different components of this pathway have provided important information regarding the physiological implication of p38α MAPK in the immune response by regulating synthesis of pro-inflammatory cytokines. This finding initiated a huge

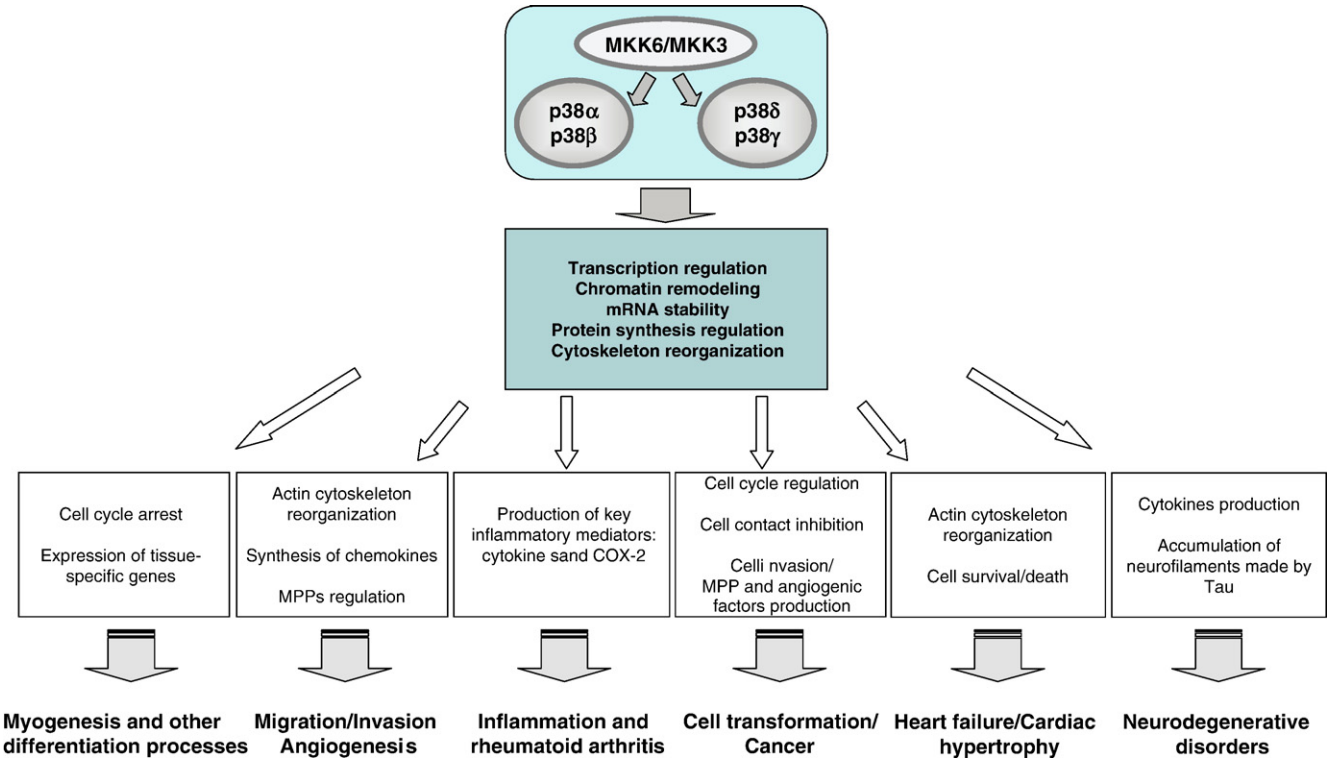

Fig. 3. Physiological roles and pathological implications of p38 MAPKs pathways. p38 MAPKs play a central role in the regulation of many biological functions, which contribute to physiological processes. Deregulation of p38 MAPKs pathways lead to the development of several pathological conditions.

effort by many companies to generate p38MAPK inhibitors as potential targets for inflammatory diseases. Recently described roles for p38 MAPK in cancer, heart and neurodegenerative diseases make this pathway highly attractive for the development of new therapeutics strategies to treat these pathologies as well. On the other hand, the role of p38MAPK in cellular differentiation, in particular its implication in the differentiation of skeletal muscle and stem cells, suggests this pathway as a potential key modulator of both tissue regeneration or cell renewal processes triggered in response to tissue lost or damaged. As highlighted in this review, the p38 MAPK pathway can have both protective and detrimental effects even in very similar systems. Thus although the p38 MAPK pathway as whole is an interesting therapeutical target, the p38 MAPK itself may not be the ideal candidate. Identification and characterization of the various substrates of these kinases involved in cell differentiation/cell proliferation, heart failure and neurodegeneration, could provide much better targets enabling the ablation of the deleterious effects while maintaining protective functions.

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